

### Remarks/Arguments

Applicants thank the Examiner for the courtesy of the in-person and telephonic interviews and for withdrawing the prior grounds for rejection.

Oath/Declaration Applicants have enclosed an amended Declaration with Dr. Eberwine's correct name and signature. This is believed to obviate this objection.

Double Patenting The Office Action rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,291,170; claims 1-14 of U.S. Patent No. 5,891,636; and claims 1 and 4-6 of U.S. Patent No. 5,545,522. When any claim is found to be allowable, the Applicants agree to file Terminal Disclaimers to U. S. Patent Nos. 6,291,170; 5,891,636; and 5,545,522.

35 U.S.C. §112, 1<sup>st</sup> Paragraph Claims 42-54 were rejected for failure to comply with the written description requirement, as not having been described in the specification so as to convey to one skilled in the relevant art that the inventor had possession of the claimed invention; in short, the claims were read as encompassing embodiments from multiple primer/promoter sets. Applicants note that independent claims 42 and 53 now recite the preparation of the claimed product with a RNA polymerase and a primer linked to an RNA polymerase promoter. This should obviate this ground for rejection.

35 U.S.C. §112, 2d Paragraph Claims 43 and 53-54 were rejected as indefinite for lack of clarity in the phrase "...amplified simultaneously with RNA polymerase and primer linked to RNA polymerase promoter..." and lack of the appropriate article before the words "primer" and "RNA polymerase promoter".

In response, Applicants have amended the language as requested by the Examiner and it is believed that this ground for rejection may be withdrawn.

35 U.S.C. §103 The Office Action rejected claims 42-54 as unpatentable over Kwoh et al. The Office Action cited Kwoh for its teaching of a Transcription-based Amplification System (TAS) to use *two* primers to amplify a given target sequence from

within a population of sequences. Applicants agree with the Office Action summary of the reference on page 13, last paragraph, and page 14, first full paragraph.

The Office Action proposed use of an “internal” standard where [presumably two] primers could be directed to a second or control sequence within the sample to “standardize” the target sequence. Applicants wish to point out that adding an internal standard to TAS is not a trivial undertaking: Not only must the sequence be chosen for similar amplification characteristics; the two primers for the control sequence also must be chosen to provide the same hybridization characteristics. In addition, Office Action proposed the use of four primers to amplify (exponentially) two sequences; whereas, the instant claimed invention is based on a single primer to amplify a plurality of native sequences. Importantly, the proposed standard nucleotide may not amplify to the same degree. This is particularly true with substituting ribosomal RNA for mRNA, as proposed by the Office Action. Moreover, such an added control is unnecessary with the instant method because the same promoter/primer complex is used with all the mRNA, thus assuring that all mRNA are amplified to the same degree and faithfully serve as internal controls. Kwoh discloses exponential amplification (“38- to 47-fold per cycle, resulting in a  $2.5 \times 10^6$  fold increase in copy number” which represents approximately  $38^4$  to  $47^4$ ) of a single nucleic acid sequence and does not teach or suggest that one amplify multiple species or linear amplification. Thus, the reference does not render the claims obvious, and Applicants respectfully request that this ground for rejection be withdrawn.

35 U.S.C. §102 The Office Action rejected claims 42-54 as anticipated by Gingeras et al. . Gingeras also teaches the TAS system of Kwoh (see above), namely, exponential expansion of the DNA samples through two cycles (page 52, line 31). Kwoh in Figure 1 shows two cycles. However, Example XI of Gingeras starts with 0.1 fm of HIV RNA and 0.1 fm  $\beta$ -globin. The Office Action states without citation that “the amplification is not logarithmic”. The Applicants did not find any data supporting such quantitation, nor do the gels appear to support that conclusion. The Office Action further alleges that amplification is linear expansion of the target and control sequence; however, the Applicants could find no mention of that feature in the detailed description.

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In fact, there is no quantitation of the data; the Figure 3 gels provide only gross comparisons. Since the Kwoh reference seems to cover the same TAS invention, and the numbers in the Kwoh abstract and other places indicate exponential expansion (see above), linear expansion appears to be inconsistent with the explicit teachings of the references. This reference fails to teach all the elements of the claims; therefore, Applicants respectfully request that this ground for rejection be withdrawn.

### **Conclusion**

Applicants respectfully request that these arguments be considered favorably and that a Notice of Allowance be issued. If the Examiner believes that a telephone call would advance the case, Applicants cordially invite the Examiner to telephone the undersigned.

If any additional fee is owed or refunded, this paper authorizes debiting or crediting to USPTO Deposit Account No. 17-0055.

Respectfully submitted,  
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